REMARKS

The application has been amended. Independent claims 1, 17 and 32 have been amended to clarify that the prefilled container is made of a composition comprising a polyolefin material and a radiation stabilizer. Additionally, claims 46-55 have been added. Support for language contained in these new claims is found at paragraphs [0008], [0020] and [0021] of the specification of the application. Accordingly, no new matter has been added. In view of these amendments and the remarks below, reconsideration is respectfully requested.

Rejection under 35 U.S.C. § 102 (b)

Claims 1-3, 8, 12-13, 16-18, 21-22, 24-25, 28-34, 36-38 and 42-43 have been rejected under 35 U.S.C. 102(b) as being anticipated by Kozimor et al. (U.S. Patent No. 6,231,936; hereinafter "Kozimor"). The Examiner asserts that Kozimor contains the following disclosures: with respect to claims 1, 17 and 32, a method of designing radiation stable, prefilled syringes that are sterilized by gamma irradiation; with respect to claims 2-3, 21-22, 33-34 and 36-37, a therapeutic drug in a container for injection into the body where the container is a bag or a syringe; with respect to claims 8, 12-13, 25, 28-29, 38 and 42-43, a container manufactured from polypropylene that includes an additional polymer at, for example, 8 weight percent; with respect to claims 30-31, a therapeutic drug in a container for injection into the body where the container is a bag or a syringe; and with respect to claims 16, 18 and 24, irradiating with gamma radiation at doses of 2.5, 5.0, 7.5 and up to 10 Mrad.

Applicants respectfully traverse this rejection and request that this rejection be reconsidered and withdrawn for the following reasons.

The present invention is directed to the surprising finding that containers constructed of polyolefin including a radiation stabilizer which are sterilized through gamma irradiation treatment will meet pharmacopoeia requirements if the container is prefilled with a medium prior to the radiation treatment. It is well-known to construct containers useful as medical devices, and particularly syringes, out of polyolefin material. Polyolefin is particularly useful in such applications due to its ease of manufacture and inexpensive raw materials. For example, polypropylene has long been used as a material of choice for manufacturing syringes. In the present invention, the container is constructed of a polyolefin composition which includes a radiation stabilizer to impart radiation stability to the container, such as those prepared in accordance with U.S. Patent Nos. 4,959,402 and 4,994,552.

However, polyolefin materials such as polypropylene are not very stable when subjected to ionizing radiation treatments, particularly gamma irradiation. Accordingly, in practice such materials typically have not been used in applications in which prefilled devices undergo terminal sterilization through gamma radiation treatment, i.e. radiation sterilization after the device has been filled. The present invention provides the unexpected finding that surprising results can be seen with respect to maintaining the integrity of a medium contained within a container through the use of radiation stable polyolefins in combination with gamma irradiation when the container is prefilled with the medium prior to such gamma irradation treatment. Thus, it is recognized through the present invention that a synergy exists between the composition of the container, the type of sterilization treatment, such as gamma irradiation, and a medium being present within the container prior to gamma irradiation. In other words, an adverse reaction of the contents of a prefilled container is inhibited during a radiation sterilization treatment by providing the container as a radiation stable polyolefin material, by prefilling the container with

a medium prior to the radiation treatment, and by using gamma radiation for the radiation treatment. Prefilling the container minimizes the reactions which incorporate radical scavengers, i.e., oxidizable substances such as hydrogen peroxide, in the container materials by providing a medium to neutralize the radical reactions during irradiation.

In contrast, Kozimor does not teach or suggest pre-filling a container with a medium prior to sterilizing the prefilled container with gamma irradiation. Rather, Kozimor teaches a radiation tolerant polypropylene material that is a blend of polypropylene and a polymer produced using single site catalysis (SSC), preferably single-site catalyzed polyethylene, which materials can be applied to the manufacture of medical devices, such as disposable and reusable hypodermic syringes. The Examiner alleges in the Office Action that Kozimor teaches irradiating syringes after they have been filled, based on Kozimor's use of the phrase "prefilled syringe," with the Examiner asserting that "irradiating prefilled syringes necessarily means syringes that have already been sealed prior to irradiation step." The passage of Kozimor identified by the Examiner (col. 8, lines 47-49), however, merely states "This would, of course, include prefilled hypodermic syringes for drug packaging and delivery as well as ancillary parts of syringes, including needle hubs and needle sheaths". Contrary to the Examiner's assertion, Kozimor never states "irradiating prefilled syringes", but instead merely identifies prefilled syringes as a type of medical device which can be made from his radiation stable material. There is nothing in Kozimor to teach or suggest the claimed invention involving sterilization after filling of the syringe. Instead, Kozimor merely lists a prefilled syringe as a product useful for the radiation stable material, without contemplating filling and then terminally sterilizing. In other words, a syringe which is to be sold as a prefilled syringe could be manufactured of a radiation stable material and radiation sterilized, prior to being aseptically

filled and then sold as a "prefilled syringe." In fact, it is common practice in the industry to construct "prefilled syringes" in this manner, with the syringe manufactured and then radiation sterilized prior to being aseptically filled, packaged, and sold as a prefilled syringe. Merely calling a product a prefilled syringe does not disclose or even remotely suggest that the product has been subjected to a terminal sterilization after filling.

In view of these remarks, it is apparent that Kozimor fails to teach, disclose, or suggest any terminal sterilization of a prefilled syringe after it has been filled with a medium, as set forth in the claims. Accordingly, withdrawal of the rejection based on this reference is respectfully requested.

Rejections under 35 U.S.C. § 103 (a)

The Office Action recites a number of additional rejections of the dependent claims under 35 U.S.C. § 103(a), based on Kozimor alone or in view of one or more additional references. In particular; claims 6-7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kozimor as applied to claim 1 and further in view of the alleged admitted state of the prior art; claims 4-5, 23 and 35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kozimor as applied to claims 1, 2, 17 and 32 and further in view of Jacobs et al (Acta Pharm, IDS; hereinafter "Jacobs"); claims 9, 14-15, 26, 39 and 44-45 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kozimor as applied to claims 8, 25 and 38 and further in view of Williams et al. (U.S. Patent No. 4,994,552; hereinafter "Williams"); claims 10-11, 27 and 40-41 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kozimor as applied to claims 8, 25 and 38 and further in view of Saito et al. (U.S. Patent No. 6,437,048; hereinafter "Saito"); and claims 19-20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over

Kozimor as applied to claim 18 and further in view of Vellutato (U.S. Patent No. 6,123,900; hereinafter "Vellutato").

Applicants respectfully traverse these rejections and request that these rejections be reconsidered and withdrawn for the following reasons.

As discussed above in detail, nowhere in Kozimor is it taught or suggested to pre-fill a syringe prior to sterilizing the syringe with gamma irradiation, and the additional references do not cure this deficiency. Jacobs has merely been cited for its teachings regarding gamma irradiation of saline water. Williams merely refers to a separate radiation stable polymer, and Saito is cited merely for its teachings with respect to a specific additive. Vellutato is cited merely for its alleged teachings regarding irradiating after packaging inside of a layered carton. None of these references, whether considered alone or in combination, disclose or even suggest that terminal sterilization of a radiation stable polyolefin material after filling the material with a medium inhibits adverse reaction of the contents of a container.

In fact, the Example 3 of the present invention demonstrates the unexpected results seen by the present invention through a comparison of syringes which have been sterilized and then aseptically filled vs. those that have been filled and then terminally sterilized. In both cases, a radiation stable polyolefin is used as the syringe material, and in both cases the final product is a prefilled syringe. However, as shown through Example 3, testing of the prefilled syringe which was subjected to terminal sterilization in accordance with the method of the present invention demonstrated marked improvement in sample quality when compared to the prefilled syringe which was irradiated and then filled.

Furthermore, Example 4 demonstrates that the type of radiation treatment in a terminal sterilization process is important to product quality, in that gamma irradiation reduces the amount of oxidizable materials in a sample as compared with E-beam irradiation.

Accordingly, a synergistic effect is realized by the present inventors through the specific container material in combination with a specific sterilization treatment with the container filled in a specific manner. None of the prior art references, whether considered alone or in combination, recognize this unexpected and surprising result.

In view of the foregoing amendments and remarks, it is respectfully submitted that all pending claims are allowable. Accordingly, reconsideration and withdrawal of the rejection and favorable action are respectfully requested.

Should the Examiner have any questions regarding any of the information contained herein or wish to discuss this matter in further detail, the Examiner is invited to contact Applicants' undersigned representative by telephone at 412-471-8815.

Respectfully submitted,

THE WEBB LAW FIRM

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